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The Proteus Syndrome: CNS Manifestations

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Summary: Proteus syndrome is a complex hamartomatous disorder characterized by multiple, diverse, somatic manifestations. We present a case in which severe, evolving CNS abnormalities were also exhibited. Imaging findings at presentation included hemimegalencephaly, subependymal calcified nodules, and periventricular cysts. Subsequently, dural sinus thrombosis developed. Eight previously reported patients may also have had hemimegalencephaly. When neuroimaging studies show hemimegalencephaly in a child with pigmented skin lesions, Proteus syndrome should be considered in the differential diagnosis.

Proteus syndrome is a complex hamartomatous disorder first described by Cohen and Hayden in 1979 (1). It was so named by Wiedemann et al in 1983 after the Greek god Proteus, who could change his form at will (2). The syndrome has multiple, diverse, somatic manifestations that evolve over time and involve the skeletal system, soft tissues, skin, and vascular system. These signs include partial gigantism of the hands and/or feet, asymmetry of the limbs, plantar hyperplasia, macrodactyly, bony exostoses, soft-tissue tumors (hemangioma, lymphangioma, lipoma), varicosities, verrucous epidermal nevi, and long-bone overgrowth (3). Although not a constant feature of the syndrome, several CNS manifestations have been briefly noted in individual cases, mainly in the genetics literature (1, 3-10). We present the imaging findings in a child with Proteus syndrome who had severe, evolving CNS manifestations, and we review the literature in an attempt to relate the abnormalities in this case to those described previously.

Case Report

A 2-year-old African-American boy presented to the pediatric genetics department of our institution at age 9 months with developmental delay and visual problems. He was the first child of nonconsanguineous parents, and the pregnancy and delivery were uneventful. On physical examination, he was large for age (95% for height and weight), had a protuberant abdomen (Fig 1A), and showed mild left ulnar deviation of the index finger. Hyperpigmented swirled and linear skin lesions were present on the face, arm, and back (Fig 1A), and verru-

cous epidermal nevi were seen on the distal extremities. Subsequent ophthalmologic examination revealed the presence of bilateral optic atrophy and a severe pigment disturbance of the retina. Laboratory studies included an abnormal electroretinogram and visual evoked response studies bilaterally; the chromosomal analysis was normal, 46,XY, on both peripheral blood lymphocytes and skin fibroblasts. Shortly after presentation, a seizure disorder developed.

Additional problems became apparent during infancy. By 16 months of age the patient was noted to have right-sided hemihypertrophy involving the face and the upper and lower extremities. Macrodactyly of the left index finger, enamel hypoplasia, and bilateral muscle atrophy of the upper extremities and shoulder girdle also became manifest (Fig 1A), as did varicosities and deep venous thromboses of the lower extremities, for which an antecedent was never found; a capillary hemangioma on the dorsum of the left foot was also noted. Abdominal sonography revealed a splenic mass, which subsequently enlarged rapidly. At splenectomy, the lesion proved to be a lymphangioma. Later, the development of scoliosis was noted.

A CT study of the head performed at 11 months of age showed hemimegalencephaly and the presence of calcified subependymal nodules adjacent to the foramen of Monro, similar to those seen in tuberous sclerosis (Fig 1B). In addition, a right frontal osteoma was identified. Follow-up MR imaging confirmed the presence of hemimegalencephaly and the subependymal nodules, and also showed periventricular cysts (Fig 1C and D). Several of the subependymal nodules appeared to enhance after administration of contrast material (Fig 1E), although it is difficult to differentiate small enhancing nodules from small internal cerebral veins present in this region. Mild cortical thickening was also seen in the contralateral cortex (Fig 1C). At 24 months of age, following worsening of the seizures, a repeat MR study showed the development of a left-sided transverse sinus thrombosis. On a subsequent study 1 month later, after anticoagulation treatment, the left dural sinus thrombosis had resolved but a right dural sinus thrombosis had developed (Fig 1F). At this writing, the child is 34 months old.

Discussion

Proteus syndrome is a complex and interesting disorder that displays multiple and diverse manifestations. After its initial description by Cohen and Hayden (1), several authors reported findings of increasing variability, which expanded the original range of possible indications. In fact, there is compel-

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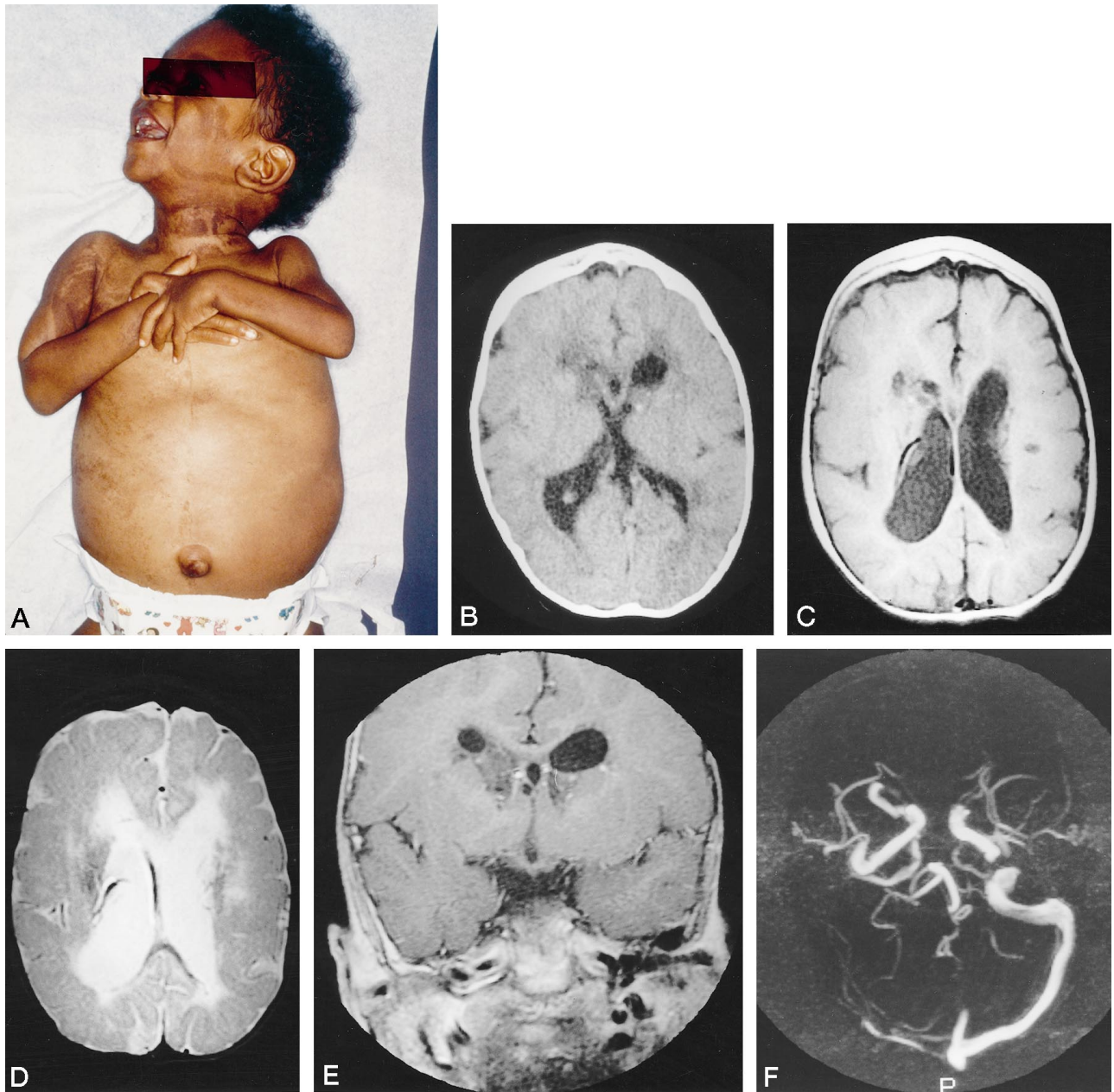


FIG 1. 2-year-old boy with Proteus syndrome.

A, Hyperpigmented linear and swirled skin lesions are evident on face and arm. Right-sided hemihypertrophy, bilateral muscle atrophy of the upper extremities and shoulder girdle, and a protuberant abdomen are also present.

B, Axial CT scan obtained at 10 months of age at the level of the basal ganglia shows asymmetry of the cerebral hemispheres and lateral ventricles. Also seen are several small, subependymal calcifications adjacent to the foramen of Monro.

C-E, Spin-echo MR examination performed at 11 months of age. Axial image (750/20 [TR/TE]) (C) shows enlargement of the right hemisphere, ventriculomegaly, and areas of macrogyria. Milder thickening of the contralateral cortex is also seen and periventricular cysts are present. Axial image (3000/80) at the same level (D) shows areas of gliosis in the white matter and mild delay in myelin deposition. Coronal contrast-enhanced image (500/12) (E) shows several areas of high signal intensity, which may represent enhancement of subependymal nodules or small internal cerebral veins.

F, Phase-contrast MR angiogram at age 25 months shows development of right transverse sinus thrombosis.

ling evidence that the renowned "Elephant man" had Proteus syndrome rather than neurofibromatosis type I (4). The syndrome is thought to occur as the result of a lethal somatic gene mutation that leads to a mosaic state that allows survival (11). This mechanism explains the sporadic occurrence, equal sex ratio, mosaic distribution of lesions, and variable extent of involve-

ment seen in this syndrome, which never completely involves the entire body or any one organ system (11).

Nearly 100 cases of Proteus syndrome have been described in the literature. From these, the frequency of mental retardation is estimated to be between 20% and 55%, and 13% of these patients are reported to have seizures (3). Some type of CNS abnormality,

detected by CT, has been described in 18 patients (1, 3–10). As many of the reported patients (including those with mental retardation and seizures) did not undergo neuroimaging, it is probable that the actual prevalence of CNS involvement in this syndrome is higher.

Frequently, multiple bony anomalies are seen in patients with Proteus syndrome, with the facial bones and calvaria commonly involved. Of the 19 cases we reviewed, 13 patients had evidence of bony exostoses of the skull and three had craniosynostoses. When craniosynostoses occurred, the coronal suture was involved in two patients and the lambdoid, sagittal, and metopic sutures in one patient each.

Development of neoplasms, which is a potential problem in all the hamartomatous syndromes, has been described in association with Proteus syndrome. Intracranially, three children reported in the literature had evidence of meningiomas and one had a pinealoblastoma (3).

Of particular interest are the associated congenital anomalies of the CNS, which have been described in 12 children: one patient had Dandy-Walker malformation, three had corpus callosal abnormalities (two absent, one thickened), and eight had evidence of hemimegalencephaly. In five of these children the diagnosis was definite, in three others it was probable (4–10). Three of these nine children, including our case, were also noted to have periventricular calcification (5, 7) and four had evidence of hypodense periventricular white matter. In addition, the brains of two children were described as atrophic.

In our case, the development of dural sinus thrombosis is noteworthy, as this child's history was negative for such predisposing factors as infection, dehydration, or the presence of an adjacent obstructing mass lesion. Although we are unaware of any other reported cases of sinus thrombosis associated with Proteus syndrome, peripheral varicosities and deep venous thrombosis have been previously reported and were also present in this case. Dural sinus anomalies have, however, been described in patients with epidermal nevus syndrome.

The CNS manifestations of Proteus syndrome share definite similarities with those of other neurocutaneous syndromes. Encephalocraniocutaneous lipomatosis, which has frequently been shown to manifest unilateral CNS findings, may represent a more localized form of Proteus syndrome (12). Affected children also commonly have mental deficiency and seizures. To our knowledge, hemimegalencephaly is not a finding in this entity; reported abnormalities include hydrocephalus, cerebral atrophy, porencephaly, cerebral calcifications, and polymicrogyria (7, 13–16).

Pigmented skin lesions, similar to those seen in our case, are also seen in association with CNS abnormalities in patients with incontinentia pigmenti and epidermal nevus syndrome (17–20). In fact, the skin lesions often cannot be distinguished. Children with incontinentia pigmenti may also have CNS manifestations, including microcephaly, hydrocephalus, and

porencephalic cysts (17–19). This entity is lethal in affected males and was, therefore, not a possible diagnosis in this instance despite the similarity of the cutaneous findings. In epidermal nevus syndrome, epidermal nevi may be seen in association with hemimegalencephaly and abnormalities of the venous sinuses. Additional CNS findings are thought to be the sequelae of vascular dysplasia, and include infarcts, atrophy, porencephaly, and calcifications (20).

Although hemimegalencephaly may be seen as an isolated entity (21, 22), it has also been described in association with cutaneous pigmentation disorders in patients with hypomyelination of Ito (23–25). This disorder was initially thought to be a neurophakomatosis, but there is now evidence that it is heterogenous in origin and frequently represents somatic mosaicism for chromosomal abnormalities (26).

Although we have no pathologic correlation for the subependymal nodules seen in our case, their appearance, location, and enhancement characteristics are reminiscent of the subependymal tubers seen in tuberous sclerosis, which is also classified as one of the hamartomatous syndromes. As in tuberous sclerosis, these lesions are situated along the subependymal surface of the caudate nucleus close to the foramen of Monro, and are calcified. If these are indeed subependymal tubers, the enhancement seen in these lesions raises the possibility that they also may undergo growth and degeneration to become giant cell astrocytomas, putting patients at risk for the development of obstructive hydrocephalus. A possible association between hemimegalencephaly and tuberous sclerosis has previously been discussed by Johnson, who described a child with both hemimegalencephaly and a cardiac rhabdomyoma (27).

The differential diagnosis of Proteus syndrome includes other more common hamartoses and causes of hemihypertrophy. When CNS involvement is apparent, however, many of these entities can be excluded and the diagnosis then consists mainly of other neurocutaneous syndromes.

Evolution and progression of clinical manifestations is the hallmark of Proteus syndrome, so that many of its later manifestations are not apparent at birth. In this particular case, during the period that the child has been followed up, the bony exostoses enlarged, hemihypertrophy and macrodactyly developed, shoulder girdle muscle hypoplasia and scoliosis became manifest, and dural sinus thromboses ensued. It is therefore possible that severely affected children who die in infancy may have acquired manifestations of CNS involvement had they lived longer.

Conclusion

Although Proteus syndrome is a rare, sporadically occurring condition, it should be considered in the differential diagnosis of children who have CNS manifestations similar to those described here in association with abnormalities of the skin, bones, or soft tissues.

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